eases in which the causative factor is not clear, such as acute rheumatic fever.

LAIRD M. MORRIS, M. D. (490 Post Street, San Francisco)—Doctor Bender presents a very comprehensive study of epidemic encephalitis. He is to be congratulated on the completeness of his paper and the manner in which it is presented. A certain interest has recently been aroused in other types of encephalitis or meningoencephalitis which attack the central nervous system in a manner similar to that of epidemic encephalitis. I refer to encephalitis following measles, mumps, vaccinia, and varicella. As presented by Doctor Bender these complications are not common, but are etiologically quite distinct from the epidemic variety. These conditions are caused by ultramicroscopic organisms, and a differential diagnosis at present is quite impossible by changes in the spinal fluid. The clinical history is therefore of paramount importance.

THE EFFECT OF LEAD UPON NORMAL AND MALIGNANT TISSUES*

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DISCUSSION *by D. Schuyler Pulford, M. D., Woodland; William Ophüls, M. D., San Francisco.*

MANY substances have been used in the treatment of malignant neoplasia, including salts of tellurium and selenium, and colloidal preparations of lead, copper, sulphur, silver, and gold. By their use regressive changes have been noted in the tumors, but in general these compounds have proved too toxic to justify general usage.

REVIEW OF RECENT LITERATURE

W. Blair Bell, to whom the credit is due for the recent interest in this problem, found that lead produces abortion by an elective toxic action on the cells of the trophoblast in animals poisoned by lead, and remarked on the frequency of abortion in lead workers.[1] He showed this to be due to coagulative necrosis of the chorionic epithelium, specific for lead and not produced by the other metals used. Working on the hypothesis that chorionic epithelium is physiologically malignant and closely related to the malignant tumors, he used lead in the treatment of these conditions.[2] He states that malignant neoplasia is a specific growth process in which there is a reversion on the part of the starving cell to the nutriment seeking proclivities of the ancestral chorionic epithelium.[3] According to the hypothesis, lead is attracted to these tissues because of the higher phosphatid values and higher phosphatid-cholesterol ratios in chorionic epithelium and malignant new growths, and that it serves as a substitute for the biological inhibitor of growth of the chorionic epithelium.[3 4] Lead was found by chemical analyses to be present in the tumor tissue out of proportion to that found in other tissues.[4]

The preparation used was colloidal metallic lead prepared by the Bredig method in 0.4 per cent aqueous gelatin with the addition of 0.027 per cent calcium chlorid.[5] The final product was centrifugalized to eliminate particles larger than 0.2 micron, made hypertonic by the addition of sodium chlorid 2.0 per cent, potassium chlorid 0.05 per cent, and calcium chlorid 0.027 per cent. The product was sterilized by boiling, and remained stable two or three days before becoming toxic. Of 227 patients treated by means of intravenous injections of the preparation, all in a hopelessly advanced stage of the disease, fifty have lived for from one to five years in a completely arrested state.

Histological evidence of the above striking effects is difficult of demonstration,[6] since microscopic examination must be made within two or three weeks of the lead injection when the regressive changes are most active. Later there should be a complete disappearance of the tumor cells, with some inflammatory reaction, and finally a replacement fibrosis. Glynn[7] urges that great caution be exercised in the interpretation of such alterations since degenerative changes commonly occur in any untreated malignancy, and reports only six instances where histological changes are demonstrable, as probably due to the lead alone. There were: distortion of the carcinoma cells into spindle, star, and sarcoma-like shapes and actual necrosis of these cells. The epithelial nature of the majority was lost. A subacute interstitial inflammatory reaction with a complete absence of tumor cells was also found. Plates of photomicrographs illustrative of these changes are given. He concluded that in the majority of lead treated malignant growths there is no histological evidence of the effect, but that in certain instances lead seemed to have increased the regressive changes which usually occur in carcinoma and to slow the rate of growth. Greater specialization of the malignant cells with keratinization and the formation of nests and goblet cells are manifestations of the slowing of the rate of growth. The lesser degree of regression found in relatively avascular fibrosed lymph glands indicates that the action of lead depends on a well-developed and unobstructed blood supply. He states that the absence of characteristic change is no proof that lead has no action, as there is nothing histologically characteristic of the effect of iodid on gummata.

Wood has observed a disappearance of malignant tumors of rats two or three days after the injection of lead suspensoids.[8] There is first an intense congestion and edema and after twenty-four hours there are abundant thromboses in the tumor capillaries with resultant necroses of the regions supplied by the affected vessels. The tumor shrinks and the tension is relieved. Unless the dose of lead has been large and repeated, however, there are usually growing cells about the periphery from which recurrences may take place. Wood believes the effect is probably pro-

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Read before the Section on Pathology and Bacteriology of the California State Medical Association Meeting at Los Angeles, April 28, 1927.

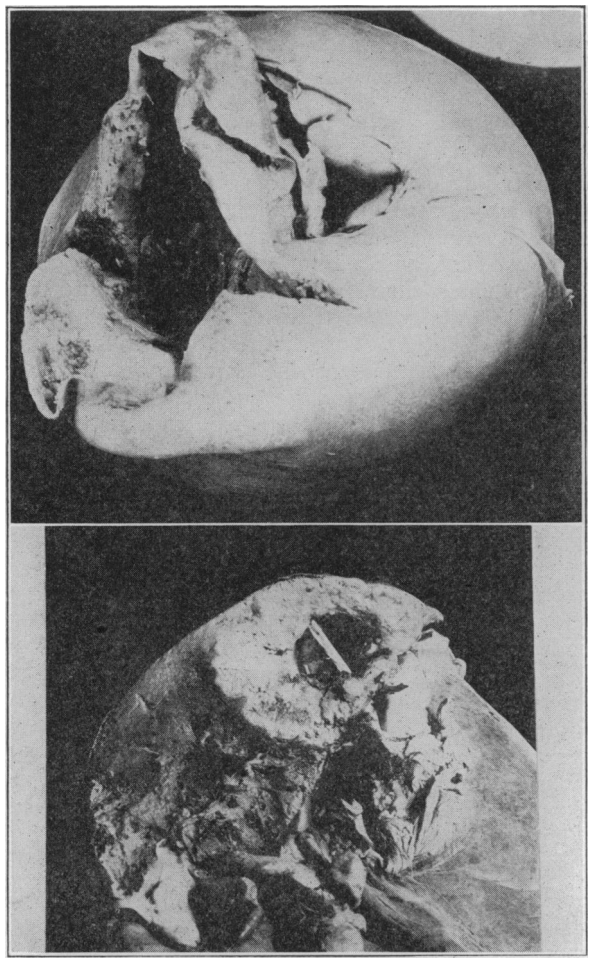

Fig 1 (top)—The cyst of the right lobe of the liver after evacuation of its liquefied contents.

Fig. 2 (bottom)—The cyst of the left lobe of the liver surrounded by a rim of tumor tissue.

duced both by capillary injury and by direct toxic action on the tumor cells.

Martland, Sochocky, and Hoffman report only one instance in seventeen in which there was unquestioned diminution in the extent of a growth possibly attributable to the lead.[9] This was an epithelioma of the lip and reduction of the inflammatory swelling might have been the explanation. They used very large doses, from 1000 to 2500 mgm. of a stable lead colloid, the details of preparation of which are not given, in doses of from 50 to 500 mgm., during a period of from six to ten weeks. They found no histological evidence that a cancer cell had taken up or absorbed lead and that no tumor contained more lead than could be explained by the difficulty in separating the tumor from the surrounding lead-containing tissue. Most of the colloidal lead was stored in the main organs of the reticulo-endothelial system by the phagocytic properties of the histiocytes of the spleen, liver, and bone marrow. They conclude that lead in the form of a stable metallic colloid does not enter into combination with the phosphatids present in carcinoma cells after intravenous administration, and that in the absence of thromboses there is no effect on malignant growths.

EFFECTS ON CERTAIN ORGANS

Liver—Marked damage of this organ may be expected since the liver eliminates lead. Alterations varying from fatty change to interlobular cirrhosis have been described in lead poisoning by Hutton, Potain, and Alcock.[10] Ophüls has produced marked focal necrosis of cells in guinea-pigs, though he believes the only condition attributable to the action of lead was the hematogenous pigmentation.[11] Aub, Fairhall, Minot, and Reznikoff agree with Oliver in that the consensus of opinion is that there is no specific change for lead.[12] Focal necroses similar to those seen in infectious diseases in human beings have been produced by Wood in rats, apparently because of vascular lesions.[8] Bell, Williams, and Cunningham noted congestion, fatty infiltration, and deposition of hemosiderin in two human beings and two dogs following the intravenous injection of colloidal metallic lead.[13]

Kidney—As evidence of damage to this organ by its excretion of lead, both the acute and chronic types of nephritis have been reported. Oliver has described acute tubular nephritis characterized by cloudy swelling and fatty degeneration of the cells lining the tubules with destruction of some.[14] Atrophy of the glomeruli with hyalin degeneration of the vessels has been seen.[15] Ophüls has seen some degeneration and fibrous thickening of the glomeruli as the only constant lesion in the guinea-pigs.[11] Cloudy swelling of the tubular epithelium was seen by Bell, Williams, and Cunningham after the use of as little as 34 mgm. and as much as 350 mgm. of lead in treatment.[13] Cloudy swelling and tubular necrosis were found by Wood in animals.[8]

Spleen—Oliver[16] believes there is no noteworthy change of this organ, and Jores has noted increased pigmentation from blood destruction.[17] A slate-brown color due to the storage of large amounts of lead in the spleen has been reported by Martland, Sochocky, and Hoffman.[9]

Blood—According to Aub and his co-authors, the changes include: punctate basophilia, polychromasia, nucleated red cells, anisocytosis, poikalocytosis, and an anemia characterized by a low hemoglobin, the red count being not much decreased.[12]

METHODS

In our own early work, colloidal metallic lead was used, prepared by the Bredig method and made resistant to oxidation by the addition of glucose.[18,21] Owing to the blood destruction produced by this compound, and since certain investigators believe that lead could hardly be present in the blood stream except as the phosphate in the colloidal form,[12] Bischoff (working in our laboratory) has prepared colloidal trilead orthophosphate.[20] Trilead phosphate in a slightly alkaline medium such as the body tissues is stable, and as such its solubility is 0.13 mgm. per liter of water. In equilibrium or in slightly acid conditions, however, dilead phosphate is formed, the

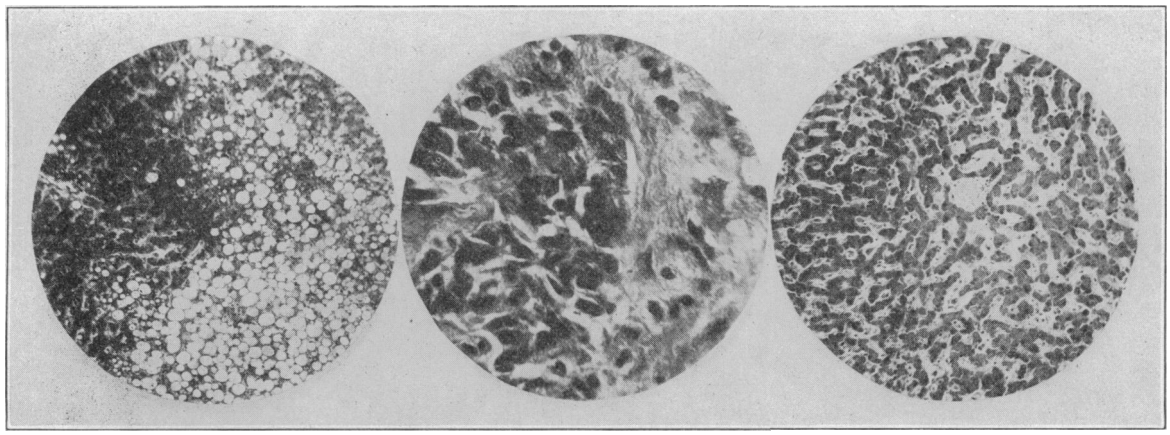

Fig. 3—Marked fatty change of the liver. (Low power.)

Fig. 4—Distorted carcinoma cells in the fibrous tissue capsule of the large cyst. (High power.)

Fig. 5—Focal necrosis of the liver. (Low power.)

solubility of which is approximately one hundred times that of the trilead salt.[12] It was hoped to take advantage of this fact to secure local toxic action within the tumor cells which have been shown to produce three to four times as much lactic acid as normal tissues.[19] The solvent action of lactic acid is specific, as certain more highly ionized acids have a less solvent effect. This of course is in contrast to the theory of Bell, who used lead on the strength of the affinity for the increased lecithin content of the tumors. The dosage and times between injections have varied with different patients and are stated for each one individually. The material includes six necropsies and two biopsies. Necropsies were made within a few hours after death and the sections were imbedded in paraffin and stained with hemotoxylin and eosin.

CASE REPORTS

PATIENT No. 1—A female, age 41 years, had an endothelioma (diagnosis concurred in by Dr. A. M. Moody of San Francisco) of the neck, excised three years before, and x-ray and radium treatments had been employed. On entrance there was a mass 5 cm. in diameter behind the left ear and metastatic nodules were seen throughout the lung fields in x-ray films of the chest. During three months 221 mgm. of colloidal metallic lead were given in approximately three equal doses. On entrance the hemoglobin was 47 per cent; the red cell count, 2,830,000, while shortly before death the former was 30 per cent, the latter 3,450,000. At necropsy the neck was found infiltrated with extension metastases and there were further metastases to the regional, mediastinal, and biliary lymph glands, and to the lungs and liver. A cyst of the dome of the right lobe of the liver was 8 cm. in diameter and filled with gray-white fluid (Fig. 1). Another of the under surface of the left lobe was 2.5 cm. in diameter with a similar content, and surrounded by a rim of tumor tissue 1.5 cm. wide (Fig. 2). Multiple small nodules up to 4 cm. in diameter were scattered throughout the lungs, and in the centers of some of them there was pus. On section of the liver there was extensive fatty change, so that from one-fourth to one-third of the liver parenchyma was replaced by fat (Fig. 3). Many small regions of tumor cells were seen in the wall of each cyst and many of these were shrunken and distorted (Fig. 4). Unaltered tumor cells were also seen. The wall of the larger cyst was mostly of fibrous tissue with but few islands of tumor tissue. In the lung the centers of the metastatic nodules were poorly stained and some were necrotic and infiltrated with polymorphonuclear leukocytes. In the spleen there was no alteration. In sections of the kidneys there was marked cloudy swelling of the cells lining the first and second portions of the convoluted tubules, and in places the lumina were obliterated. In small regions actual necrosis of these cells had occurred.

PATIENT No. 2—A male, age 51, had noticed blood in the stools and loss of weight for six months. An annular indurated mass was palpable high in the rectum that bled easily. During twelve weeks 251.2 mgm. of colloidal metallic lead were given intravenously in three doses. The hemoglobin dropped from 78 to 48 per cent, the red cell count from 4,750,000 to 3,310,000. The anatomic diagnoses were: carcinoma of the rectum with regional extension into the wall of the left ureter, and metastases to the lungs, omentum, and peritoneum; multiple abscesses of the lungs (liquefaction of the carcinomatous areas and secondary infection); bilateral hypostatic bronchopneumonia; terminal subacute peritonitis and pericarditis; moderate left hydroureter and hydronephrosis; cloudy swelling of the kidneys; and moderate hyperplasia of the spleen. An abscess cavity of the left lung was 6 x 3 cm. and filled with thick creamy pus, and two others in the hilus of the right lung were 1 cm. in diameter. Thick fibrous walls surrounded these cavities. In sections of the liver multiple regions of focal necrosis interrupted the continuity of the cords of cells (Fig. 5). Only a moderate amount of fatty change was present. In the tumor nodules of the lungs the centers were poorly stained if at all. There was no noteworthy change of the spleen. The changes in the kidney were those of a chronic glomerulo nephritis with thickening of Bowman's capsule. Of the cells of the convoluted tubules there was cloudy swelling, and of some there was actual necrosis. In 100 gm. of tissue from the lung, liver, and carcinoma, there were found 0.96, 0.60, and 0.21 mgm. of lead respectively.

PATIENT No. 3—A male, 40 years of age, complained of loss of weight, weakness, and an enlarging mass of the abdomen for three months. A laparotomy had revealed an extensive carcinoma of the liver. Fifty mgm. of colloidal metallic lead and 52 mgm. of colloidal lead phosphate were injected intravenously at an interval of seventeen days. The hemoglobin on entrance was 80 per cent and just before death was 75 per cent, while the red cell counts were 4,210,000 and 4,150,000, respectively. The anatomic diagnosis included: extensive carcinoma of the liver with metastases to the pancreas, lungs, endocardium, epicardium, left kidney and subcutaneous tissue; hydrops; icterus; and cloudy swelling of the kidneys. The liver weighed 4392 gm. and was infiltrated with tumors varying in diameter from 5 mm. to 22 cm. In the large tumors there was some evidence of softening in the centers. In sections of the nodules of the liver the cells were

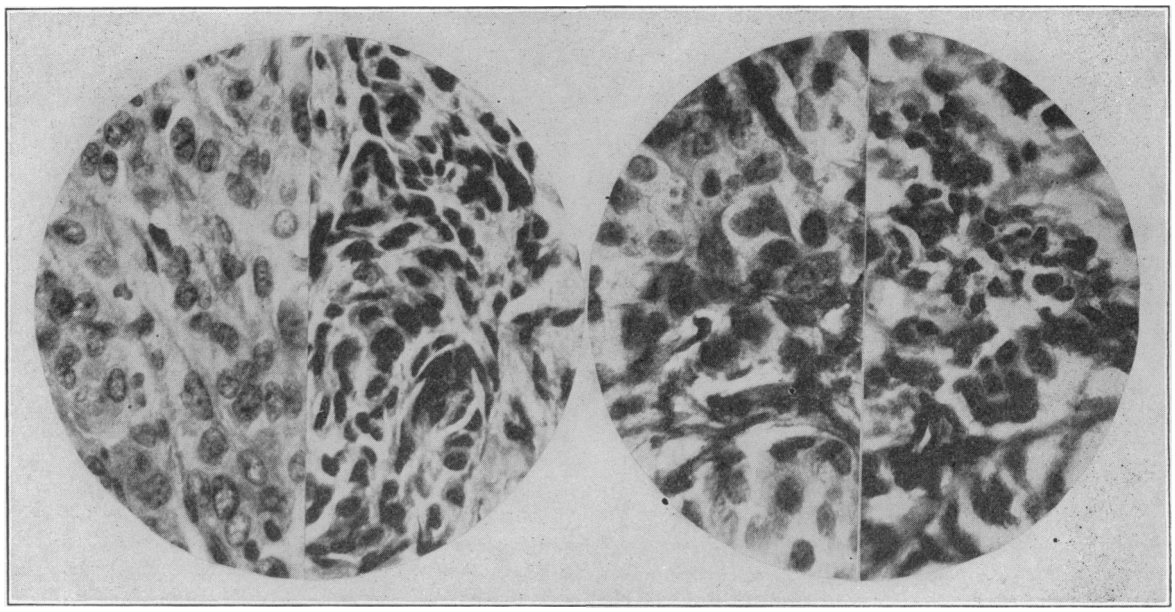

Fig. 6—On the left hand are the "healthy" carcinoma cells, while on the right they are distorted by direct injection of colloidal lead phosphate. (High power.)

Fig. 7—At the left are apparently healthy carcinoma cells from the center of a subcutaneous nodule treated only by intravenous colloidal lead phosphate. At the right are altered tumor cells from the periphery of the same nodule. (High power.)

atypically epithelial, with hyperchromatic nuclei and poorly staining cytoplasm. No change attributable to the lead was present. Practically all of the liver was replaced by tumor tissue. During life 0.5 cc. of colloidal lead phosphate (containing 2 mgm. of lead) was injected directly into the center of a subcutaneous nodule of the left elbow, and two days later this nodule and a similar sized one overlying the sternum were excised. In sections of the latter the carcinoma cells were round and appeared "healthy," while in those of the former into which the lead was injected, the cells were markedly distorted into bizarre shapes and were barely recognizable as epithelial cells (Fig. 6).

PATIENT No. 4—A male, age 69 years, had complained of difficulty in urination for eighteen months, with loss of weight and hypogastric pain. By rectal examination a large mass the size of a tangerine, nodular and tender, was felt arising from the prostate gland. During five weeks 280 mgm. of lead phosphate were given in three doses. After the second dose the mass had reduced one-third in size and there was much less tenderness. The hemoglobin fell from 55 to 45 per cent, the red cell count from 3,300,000 to 2,900,000 during the last eight weeks of life. The anatomic diagnoses were: carcinoma of the prostate gland with metastases to the lumbar lymph glands; bilateral hydronephrosis; right bronchopneumonia and serofibrinous pleuritis. There was practically nothing but carcinoma tissue in sections of the prostate gland with the cells arranged in poorly formed alveoli and solid masses. Mitotic figures were common and no degenerative changes were evident. In the liver there was no evidence of damage. In the lung the alveoli of the consolidated portion were filled with an inflammatory exudate. There was moderately increased deposition of pigment in the spleen. By chemical analyses of 100 gram weights of tissues there were: in the liver, 1.93 mgm. of lead; in the sternum, 0.52 mgm. of lead; in the lung, 0.13; in the kidney, 0.14; and in the carcinoma itself, 0.36 mgm. of lead.

PATIENT No. 5—A male, age 69 years, complained of difficulty in swallowing for two years and had had x-ray treatments. Over a period of four weeks 144 mgm. of colloidal metallic lead were administered in three doses. The hemoglobin fell from 80 to 70 per cent, the red cells from 4,500,000 to 2,930,000. An occasional stippled cell was present. The main features of the anatomic diagnosis were: carcinoma of the esophagus with obstruction and metastases to the regional lymph glands; gastrostomy, terminal left hypostatic bronchopneumonia; hypostatic hyperemia and edema of the lungs; long-since surgically removed prostate gland; and slight left hydronephrosis. The wall of the esophagus for 5 cm. of its lower third was thickened up to 15 mm. with firm gray tissue so that the tip of a finger could barely be passed through the lumen. In sections of the esophageal wall the cancer cells were without evidence of degenerative change. In those of the kidneys there was a moderate grade glomerulo nephritis with hyalinization of some of the glomeruli. There was no evidence of change attributable to lead. In sections of the liver and spleen there were no changes. In 100 gm. of sternum, 0.66 mgm. of lead was found by chemical analysis; in a like amount of diaphragm, 0.42 mgm. of lead.

PATIENT No. 6.—A female, age 65 years, complained of vaginal discharge and pelvic pain for six weeks. A hard mass about the cervix and upper half of the vagina was found to extend into the left broad ligament. Deep x-ray therapy was used in conjunction with radium. On entrance the hemoglobin was 70 per cent, the red cell count 3,380,000; just before death the figures were 43 per cent and 3,250,000 respectively. Two hundred and fifty mgm. of colloidal lead phosphate were injected in three doses during the course of five weeks. Three months later 80 mgm. of lead phosphate were given. The anatomic diagnoses included: carcinoma of the urinary bladder, with metastases to the vagina; left hydroureter and hydronephrosis; right nephrolithiasis and pyonephrosis. In sections of the tumor there were small solid masses of epithelial cells free from degenerative changes. In the liver there were slightly fatty change, and a few regions of focal necrosis. There was cloudy swelling of the cells lining the convoluted tubules of the kidneys, and the deposition of pigment in the spleen was moderately increased.

PATIENT No. 7—A female, age 44 years, had had a radical resection of the left breast three and one-half years before for carcinoma, and later subcutaneous nodules were removed on two occasions. In all 340 mgm. of colloidal lead phosphate have been administered intravenously during five months, and x-ray and radium therapy have been used in conjunction.

Marked regression of a large carcinoma of the right breast and of subcutaneous nodules has been observed. In a section of a subcutaneous nodule removed during life which had not been radiated, the carcinoma cells in the center were round and apparently "healthy," while those about the periphery were markedly distorted and similar to those of the nodules previously described into which lead had been directly injected (Fig. 7).

Chemical Analyses

Tissue	Mgm. of Lead Per 100 Gm.	Lead Administered to Patient
Patient No. 2:		
Lung	0.96	252 mgm. of colloidal metallic lead
Liver	0.60	
Carcinoma	0.21	
Patient No. 4:		
Liver	1.93	280 mgm. of colloidal lead phosphate
Sternum	0.52	
Lung	0.31	
Kidney	0.14	
Carcinoma	0.36	
Patient No. 5:		
Sternum	0.66	149 mgm. of colloidal metallic lead
Diaphragm	0.42	

SUMMARY

In a short series of patients where all available means to combat the disease have been employed, including blood transfusion, x-ray and radium therapy, it is difficult to evaluate the results. The following statements seem fair:

1. Marked regressive changes have been noted in certain of the tumors treated by intravenous preparations of colloidal lead.

2. Fatty change of the liver, cloudy swelling of the cells lining the convoluted tubules of the kidneys, and blood destruction are changes fairly constantly associated with the use of colloidal metallic lead.

3. Our observations bear out the statement of Glynn that there is nothing histologically pathognomonic of the effect of lead on tumor cells, but that the naturally occurring regressive changes are intensified.

Santa Barbara Cottage Hospital.

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DISCUSSION

D. Schuyler Pulford, M. D. (Woodland Clinic, Woodland)—The Blair Bell idea of neoplasia is not new. It has been thought for a long time that the non-communistic invasive growth of tumor cells was a food-searching activity, the result of an unsatisfactory environment. MacCarty has clearly described this process of neoplasia in terms of degrees of differentiation, 0°-1°-2°-3°, recognizing the "reserve cell" which has "gone wild" as the start of it all. Many organs have been shown to possess this reserve cell lying in the membrana propria and springing into life on certain stimuli to produce new cells such as in repair when adult functioning cells are destroyed, or for some unknown reason producing a benign neoplasm. Sometimes, perhaps after continued insult of a chronic irritant, a malignant invading metastasizing neoplasm is produced, not by a "reversion," but by an accentuation of the normal growth process.

I mention MacCarty's idea of 0°-1°-2°-3°, of differentiation in neoplasia because it is the principle which enables one to classify all new growths in the way most important to both the patient and the doctor; that is to say, in terms of its degree of malignancy. A new growth with 0 degree differentiation is the most malignant tumor possible; 1 degree and 2 degrees differentiation are the commonly encountered malignant neoplasms. Three-degree type are bnign tumors.

For the sake of clarity in discussing the grading of neoplasms, which I believe is important in the study of the lead treatment of tumors, let me emphasize that this 0°-1°-2°-3° differentiation is applied to neoplasia, the development of new growths, and is not applied to the classification of neoplasms or the grading of tumors after being developed.

The grading of tumors is spoken of in four grades—1, 2, 3, 4—in ascending grades of malignancy according to the differentiation in the cells of the tumor as such. Given a malignant tumor it is graded princi-

pally by a simple mathematical estimation of the per cent of differentiated cells per field.

Now since cell growth is directly proportional to lack of differentiation, and since cell vulnerability to destructive agents is likewise proportional to this, it must be an important factor in deciding the efficacy or failure of lead treatment. And I believe that it will help to clarify matters if the grade of malignancy of the tumors be reported after this method of Broders.

Since we have so little knowledge of the etiology of cancer it is well to concentrate upon its treatment. The latest and most promising line of attack is the Blair Bell-Ullmann colloidal tri-orthophosphate lead treatment. Our knowledge of the effect of colloidal lead upon normal and malignant tissues is still meager, and this accurate description of organs and tissues removed before death and at autopsy commands the attention of all interested in the fight against malignant disease.

It is the experience of the Woodland Clinic in four treated cases, including one autopsy, that the tri-lead orthophosphate solution as made by Bischoff of the Santa Barbara Cottage Hospital is very slightly toxic upon normal cells though destructive to malignant ones and does not produce the marked blood changes of the earlier Bredig prepared colloidal lead solutions. Our autopsy case was a Grade IV carcinoma of the stomach in a middle-aged Japanese man who had extensive recurrent nodules in the abdomen, mediastinal and cervical lymph nodes, and lung and liver metastases. He was given 390 mgms. of colloidal lead during a period of six weeks. The striking features were relief of pain, definite reduction in size of tumors and lack of anemia. Kidney function remained good. There was no jaundice. At autopsy neither kidney nor liver showed gross or microscopic parenchymal change though there were two nodules in the liver, 5 and 4 cm. in diameter, and many smaller nodules in the same organ. The lung metastases were broken down into abscesses. The liver function test done just before death showed a dye retention II on a scale of I to IV after the bromosulphphthalein colorimetric method.

We have under treatment at present, besides an advanced cystadenoma of the ovary with large abdominal metastases, two patients in excellent general condition, one a Grade IV carcinoma of the breast and the other a squamous cell epithelioma of the jaw, Grade III.

Radiation is being utilized in all cases, and it appears to me that an added value of this procedure should be noted. If the lead is concentrated in the malignant tissue secondary irradiation would then be intensified and a greater depth dose could be given.

The excision of metastatic nodules for study during the course of treatment will be valuable, as well as direct injection of colloidal lead into the tumor masses as reported. This paper is, in my opinion, a very important and far-reaching contribution which will be most helpful to anyone undertaking the lead treatment of malignancy. As far as we have gone we agree with the Santa Barbara group and with Glynn that there is nothing characteristic of the effect of lead upon either normal or malignant cells morphologically demonstrable by our present known methods. It would seem that the solution of the problem lies more in the field of biophysics rather than tissue pathology. The liver function test may help in checking the administration of lead up to the point of such marked fatty replacement as described by the authors.

I believe that the Santa Barbara Clinic has proven that their colloidal tri-orthophosphate solution of lead is sufficiently non-toxic to be used safely in the hands of those equipped to follow the chemistry of the patients carefully, and that it should be used earlier in the course of malignant disease. It should especially be used in the Grade IV carcinomas with the patients in good general condition at the time diagnosis is made, because Grade IV cases practically invariably ultimately die of recurrence under the older means of treatment.

I would like to ask the authors how soon and how late kidney damage has appeared in their cases under the administration of their present colloidal tri-orthophosphate lead solution. Our autopsy case received 390 mgms. of lead and showed no kidney change either functionally or morphologically, death occurring two months after the first injection from toxic asthenia. Our breast case has received 153 mgms. in three weeks and is now a month from the first injection and still maintains normal amount of urine and function of kidney.

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W. OPHÜLS, M. D. (Stanford University Medical School)—Doctor Nuzum's paper on the effect of lead upon normal and malignant tissues has interested me very much, because some time ago I made a study on chronic lead poisoning in guinea-pigs. The experiments were carried on by feeding a series of twenty-eight guinea-pigs carbonate of lead in sublethal doses. Some of the animals remained under the influence of lead for more than three years. The most pronounced changes were observed in the blood and the bone marrow. The animals became very anemic, had many nucleated reds in the circulating blood and the severe damage to the bone marrow was indicated by the appearance of megaloblasts in the marrow and in the circulation. The chief lesions in the kidneys and liver were focal necroses of the epithelial cells. In the kidneys they were located in the distal parts of the convoluted tubules and in the liver they were scattered irregularly in the liver lobules. The destroyed cells in both organs were replaced by regenerative proliferation of the remaining normal cells. In course of time the regenerative process became insufficient. This occurred relatively rarely in the kidneys, more frequently in the liver. The result of this insufficient regeneration was a collapse of the tissues in the affected areas. Few small areas of collapse were observed in the kidneys, many large ones in the liver. As a result of this in the late stages of the poisoning the liver was often greatly deformed. Little connective tissue proliferation took place in either organ and the vascular and glomerular changes were insignificant. No thromboses were observed in the blood vessels. The only vascular change which was fairly constant was an increased permeability of the capillary blood vessels which caused the production of aseptic serofibrinous exudates in the serous cavities.

From these experiments it is quite evident that lead is a primary cellular poison to which the red blood cells, also the liver cells, are very susceptible and to a lesser extent the renal epithelium. It is therefore quite possible that lead may have a similar or even more pronounced destructive action on tumor cells. I must confess that, to my mind, the evidence brought forward to support this view is more suggestive than entirely convincing. Central degeneration and softening of tumor nodules is nothing unusual in untreated cases. Spontaneous regressions of tumors are observed from time to time. Histologically it is very unusual to find a malignant growth in which not at least part of the cells are degenerated or actually necrotic. It is only by the comparative observation of long series of cases that Doctor Nuzum's contention, that by the lead treatment the naturally occurring regressive changes are intensified, can be finally substantiated. In the meantime it is certainly desirable that all cases which have been carefully observed clinically and have been subjected to a searching post-mortem examination should be published.

Doctor Pulford's suggestion that particular attention should be paid to the natural degree of malignancy of the tumors treated, is a good one. It should be understood, however, that it is not always an easy matter to make this determination. The primary tumors vary from time to time in the rate of their growth; their metastases sometimes grow more, sometimes less rapidly than the original tumors; each

individual tumor nodule usually has a slowly growing or even stationary center and a more actively growing periphery with varying grades of proliferative activity in between. It is not very practical, therefore, to express the grades of malignancy on a mathematical basis, but it is possible by taking into account the clinical as well as the histological picture to classify them roughly under the headings: very malignant, moderately malignant, relatively benign, and benign.

TRAUMATIC THROMBOSIS OF THE UPPER EXTREMITIES*

By JOSEPH K. SWINDT, M. D.

Pomona

DISCUSSION *by C. Latimer Callander, M. D., San Francisco; Harlan Shoemaker, M. D., Los Angeles; Charles T. Sturgeon, M. D., Los Angeles.*

AN acute thrombosis of the subclavian and axillary veins subsequent to effort has been recognized for forty years, but comparatively few cases have been placed on record. As there have been no autopsies and only a few biopsies, the establishment of indirect traumatism as the causative factor has been left to a forensic discussion of the unsettled theories of thrombus formation in general.

A survey of the literature reveals about fifty cases which have followed unaccustomed activity of the arms. The composite picture which they present is so distinct that the recognition of traumatic thrombosis as a definite clinical entity seems to be fully justified.

A typical case is characterized by Lowenstein as follows: "Following slight or more marked exertion, but without direct injury to the vein, there is a progressive swelling of the arm with pain usually referred to the axilla. With the increase of edema there are evidences of collateral circulation, and cyanosis is of frequent occurrence, although pallor may be present. Palpation of the axilla reveals a hard indurated cord, sensitive to pressure. The development of these phenomena usually occurs without fever and is succeeded by a period of rapid or more often tardy retrogression. This summarizes the history of a typical case of 'thrombose par effort,' 'a spontaneous thrombosis following exertion.'

The effort which produces this type of thrombosis seems to be, in the first place, an oft-repeated or prolonged exertion and, in the second place, one to which the patient is unaccustomed. In this way a sort of chronic trauma is applied indirectly to the vein which is quite different from the acute trauma of contusions and fractures which is applied directly to the vein. Willan's three cases were in athletic men who engaged in heavy labor; Scheppelmann's patient was riding a wild horse; Baum's case was a housewife who had been moving heavy furniture; Rosenthal's were in a woman beating clothes and a child playing ball; Lowenstein's patient carried heavy trays for two hours while waiting on tables; Winterstein's was a weaver who piled heavy bolts of cloth on shelves above his head. My case occurred in a muscular young man "pulling tents" with a citrus fumigating gang. These tents are lifted from the trees by means of long poles and the effort required is extreme, with the arms held high above the head.

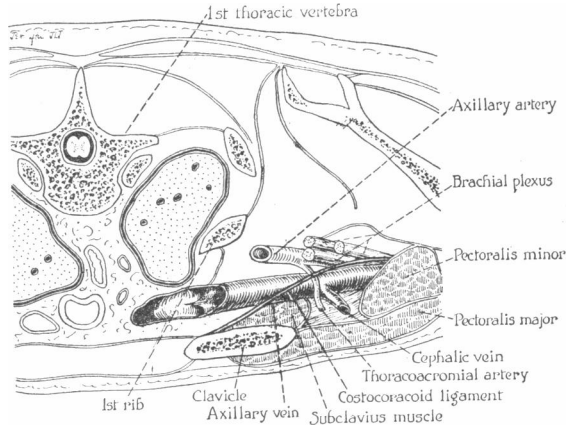

Fig. 1—Upper surface of transverse section at the level of first thoracic vertebra (lower third). Male adult. (Lowenstein.)

The majority of the cases reported have occurred in members of the working class in pursuance of their regular occupation, but called upon to perform some unusual duty, as in the case of the foreman of the tent-pullers taking the place of a sick laborer, or the weaver compelled to hastily pile the heavy bolts of cloth. Certain predisposing factors, such as substernal goiter, intrathoracic aneurysm or tumor, tuberculosis, syphilis, other chronic and acute infections may be present. Regardless of the presence of such predisposing factors it appears that chronic trauma is not incidental but absolutely essential to the production of the variety of thrombosis under consideration. It therefore follows that insofar as the trauma is the result of industrial activity, in all fairness to the injured employee, the lesion should be classed as an industrial accident and as such it should fall within the coverage of industrial compensation.

RÔLE OF INFECTION

Infection has so long been fixed in the minds of the profession as the primary cause of thrombosis that it is difficult to controvert the opinion of Lacene that the lesion is to be explained on the basis of a latent thrombophlebitis of bacterial origin. Most of the cases of thrombosis through effort have not been initiated by chills, their course has not been attended by fever, there has not been leukocytosis and other evidence of infection, and in many instances negative blood cultures have been reported. While Grimalt removed a clot from between ligatures and recovered staphylococcus albus and streptococcus viridens, Scheppelmann incised a thin-walled axillary vein and delivered an aseptic clot. Twenty years ago Welch said, "The problem whether bacteria have led to thrombosis by first invading the vascular wall and setting up an inflammation is not solved by the mere demonstration of their presence in

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